

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. 99N-4490]

Additions to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

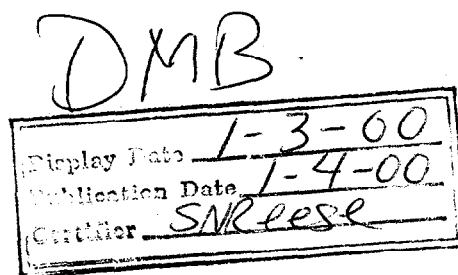
SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to add two drug products to the list of drug products that may not be used for pharmacy compounding under the exemptions provided by the Federal Food, Drug, and Cosmetic Act (the act) because they have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective.

DATES: Written comments must be received on or before (*insert date 75 days after date of publication in the Federal Register*).

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Wayne H. Mitchell, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:



I. Background

President Clinton signed the Food and Drug Administration Modernization Act (Public Law 105-115) into law on November 21, 1997. One of the issues addressed in the legislation is the applicability of the act to the practice of pharmacy compounding. Compounding involves a process whereby a pharmacist or physician combines, mixes, or alters ingredients to create a customized medication for an individual patient. Section 127 of the Modernization Act, which adds section 503A to the act (21 U.S.C. 353a), describes the circumstances under which compounded drugs qualify for exemptions from certain adulteration, misbranding, and new drug provisions of the act (i.e., sections 501(a)(2)(B), 502(f)(1), and 505 of the act (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)).

Section 503A of the act contains several conditions that must be satisfied for pharmacy compounding to qualify for the exemptions. One of the conditions is that the licensed pharmacist or licensed physician does not “compound a drug product that appears on a list published by the Secretary in the **Federal Register** of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective.”

II. Rulemaking to Establish the List

In the **Federal Register** of October 8, 1998 (63 FR 54082), we proposed the original list of drug products that have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. We published the original list as a final rule in the **Federal Register** of March 8, 1999 (64 FR 10944). You may wish to read these documents for additional information about the list. The two **Federal Register** documents may be found on the Center for Drug Evaluation and Research’s website at <http://www.fda.gov/cder/pharmcomp/default.htm> or the Government Printing Office’s website at http://www.access.gpo.gov/su_docs/aces/aces140.html.

The list was codified as § 216.24 of Title 21 in the Code of Federal Regulations (CFR) (21 CFR 216.24). This is the first time we have proposed to amend the list.

III. Description of this Proposed Rule

We are proposing that the drug products described below be added to the list of drug products that have had their approval withdrawn or were removed from the market because the drug product or its components have been found to be unsafe or not effective. Compounding a drug product that appears on the list is not covered by the exemption provided in section 503A(a) of the act, and it may be subject to enforcement action under sections 501(a)(2)(B), 502(f)(1), and 505 (among other applicable provisions) of the act.

Aminopyrine: All drug products containing aminopyrine. Drug products containing aminopyrine were used as an analgesic and an antipyretic. Aminopyrine caused agranulocytosis, a condition characterized by a decrease in the number of certain white blood cells and lesions on the mucous membrane and skin. Some of the cases of agranulocytosis were fatal. In 1964, we declared drug products containing aminopyrine to be new drugs. We invited new drug applications (NDA's) for these drug products, but only for use as an antipyretic in serious situations where other safer drugs could not be used (see 21 CFR 201.311 (42 FR 53954, October 4, 1977)). We received no NDA's for drug products containing aminopyrine, and those unapproved drug products were removed from the market by their manufacturers (see 42 FR 53954).

Astemizole: All drug products containing astemizole. Astemizole tablets were marketed under the trade name Hismanal and were indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. We approved the NDA for astemizole tablets in December 1988. Within a few years of the approval, it was learned that low-level overdoses of astemizole were resulting in life-threatening heart arrhythmias. Patients with liver dysfunction or who were taking other drugs that interfered with the metabolism of astemizole were also found to be at risk of serious cardiac adverse events while taking astemizole. The manufacturer of astemizole tablets, the only astemizole drug product, removed the product from the market on

June 18, 1999. We published a notice in the **Federal Register** of August 23, 1999 (64 FR 45973), announcing our determination that astemizole tablets were withdrawn from the market for safety reasons.

IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including having an annual effect on the economy of \$100 million or adversely affecting in a material way a sector of the economy, competition, or jobs, or if it raises novel legal or policy issues. As discussed below, the agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The agency has not estimated any compliance costs or loss of sales due to this proposed rule because it prohibits pharmacy compounding of only those drug products that have already been withdrawn or removed from the market. Although the agency is not aware of any routine

use of these drug products in pharmacy compounding, the agency invites the submission of comments on this issue and solicits current compounding usage data for these drug products.

Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant economic impact of a regulation on small entities. The agency is taking this action to comply with section 503A of the act. This provision specifically directs us to develop a list of drug products that have been withdrawn or removed from the market because such products or components have been found to be unsafe or not effective. Any drug product on this list will not qualify for the pharmacy compounding exemptions under section 503A of the act.

The drug products that are proposed to be added to the this list were manufactured by several different pharmaceutical firms, some of which may have qualified under the Small Business Administration (SBA) regulations (those with less than 750 employees) as small businesses. However, since the list only includes drug products that have already been withdrawn or removed from the market for safety or efficacy concerns, this proposal will not negatively impact these small businesses. Moreover, no compliance costs are estimated for any of these small pharmaceutical firms because they are not the subject of this rule and are not expected to realize any further loss of sales due to this proposal. Further, the SBA guidelines limit the definition of small drug stores or pharmacies to those that have less than \$5.0 million in sales. Again, the pharmacies that qualify as small businesses are not expected to incur any compliance costs or loss of sales due to this regulation because the products have already been withdrawn or removed from the market, and the agency believes that these drugs would be compounded only very rarely, if ever. Therefore, we certify that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202 of the Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any expenditure by State, local, and

tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year. The publication of the list of products withdrawn or removed from the market because they were found to be unsafe or ineffective will not result in expenditures of funds by State, local, and tribal governments or the private sector in excess of \$100 million annually. Because the agency does not estimate any annual expenditures due to the proposed rule, we are not required to perform a cost/benefit analysis according to the Unfunded Mandates Reform Act.

VI. Paperwork Reduction Act of 1995

We tentatively conclude that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before (*insert date 75 days after date of publication in the Federal Register*), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 216

Drugs, Pharmacy compounding, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 216 be amended as follows:

PART 216—PHARMACY COMPOUNDING

1. The authority citation for 21 CFR part 216 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 355, and 371.

2. Amend § 216.24 by adding alphabetically to the list of drug products “Aminopyrine” and “Astemizole” to read as follows:

§ 216.24 Drug products withdrawn or removed from the market for reasons of safety or effectiveness.

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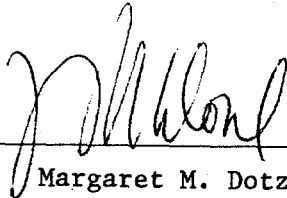


Aminopyrine: All drug products containing aminopyrine.

Astemizole: All drug products containing astemizole.

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Dated: 12-10-99
December 10, 1999



Margaret M. Dotzel
Acting Associate Commissioner for Policy

[FR Doc. 99-???? Filed ??-??-99; 8:45 am]

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